UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/776,757 | 02/11/2004 | Michel Pairet | 01-1174-1-C1 | 3466 |

28519 7590 12/21/2010

MICHAEL P. MORRIS
BOEHRINGER INGELHEIM USA CORPORATION
900 RIDGEBURY RD
P O BOX 368
RIDGEFIELD, CT 06877-0368

| EXAMINER | |
|---|---|
| BADIO, BARBARA P | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1628 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 12/21/2010 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTO.e-Office.rdg@boehringer-ingelheim.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 10/776,757
Filing Date: February 11, 2004
Appellant(s): PAIRET ET AL.

John Sopp
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed October 4, 2010 appealing from the Office action mailed May 19, 2010.

**(1) Real Party in Interest**

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The following is a list of claims that are rejected and pending in the application:

Claims 1, 3, 4, 9, 10, 15-17, 19-21, 23, 25, 26, 31-37, 39 and 63-66 are pending and stand rejected.

**(4) Status of Amendments After Final**

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

**(5) Summary of Claimed Subject Matter**

The examiner has no comment on the summary of claimed subject matter contained in the brief.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the

subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

**(7) Claims Appendix**

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

**(8) Evidence Relied Upon**

| | | |
|---|---|---|
| 6,645,466 | KELLER et al. | 11-2003 |
| 5,610,163 | BANHOLZER et al. | 3-1997 |
| 00/28979 | KELLER et al. | 3-2000 |

Nishimura et al., "Additive Effect of Oxitropium Bromide in Combination with Inhaled Corticosteroids in the Treatment of Elderly Patients with Chronic Asthma", Allergology International, vol. 48, (March 1999), pages 85-88.

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

(I) **Claims 1, 3, 4, 9, 10, 15-17, 19-21, 23, 25, 26, 31-37, 39 and 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nishimura et al. (Allergology International, 1999) and Banholzer et al. (US 5,610,163) in combination.**

Nishimura et al. teaches an inhalation composition comprising anticholinergic agents, such as, oxitropium bromide and ipratropium bromide and corticosteroids such as beclomethasone dipropionate for treating asthma (see the entire article, especially page 85, col. 2, Introduction; page 87, Table 1 and Discussion). Nishimura teaches the

addition of oxitropium bromide to beclomethasone dipropionate shows beneficial effects (see page 87, col. 1, Discussion, 1st paragraph).

Banholzer et al. teaches thienyl carboxylic acids such as tiotropium and its salts as strong anticholinergic agents having prolonged action for use in treating asthma (see the entire article, especially col. 3, line 23 - col. 4, line 9; col. 5, compound A). Banholzer also teaches the compounds show similar toxicity to ipratropium bromide while at the same time the therapeutic effect is stronger and prolonged (see col. 3, lines 27-32).

The combination of the above cited references makes obvious the utilization of a composition comprising an anticholinergic agent, including tiotropium bromide and a corticosteroid, including beclomethasone dipropionate in the treatment of asthma. The motivation to combine an anticholinergic agent with a corticosteroid is based on the teaching by Nishimura of the beneficial effect of said combination. The motivation to utilize tiotropium salts in said composition is based on the teaching of Banholzer of the increase therapeutic effect over ipratropium bromide.

The recitation of (a) ciclesonide (see claims 1 and 39); (b) weight ratios of anticholinergic to steroid (see claims 9 and 10); (c) particle size of excipients (see claims 15-17, 19-21); (d) capsule containing the claimed composition (see claims 25, 26, 31-37) and (e) a kit containing the claimed composition (see claims 63-66) are noted.

However, (a) Nishimura broadly teaches the use of corticosteroids and ciclesonide is a well known corticosteroid in the art and (b) Banholzer teaches various formulations including capsules (see '163, col. 4, lines 3-9). Additionally, the recitation

of particle size; weight ratio of the active ingredients and kits are not patentable over the cited prior art because (a) the court has held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 105 USPQ 233 and (b) incorporation of known agents into kits are well known in the medical art. Therefore, the instantly claimed invention would have been obvious to one of skilled in the art at the time of the present invention.

II) **Claims 1, 3, 4, 9, 10, 15-17, 19-21,23, 25, 26, 31-37, 39 and 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keller et al. (WO 00/28979, see English equivalent US 6,645,466), Nishimura et al. (Allergology International, 1999) and Banholzer et al. (US 5,610,163) in combination.**

Keller et al. teaches dry powder formulations for inhalation (see the entire article, especially claims 1-11; Example 6). Keller also teaches (a) preferred dry powder formulations containing a β-mimetic and/or an anticholinergic and/or a corticosteroid (see for example, col. 6, line 52 - col. 7, line 10); (b) the use of known carriers for the preparation of dry powder formulations such as glucose, lactose, sucrose, etc. (see col. 8, lines 1-16); (c) anticholinergics such as tiotropium bromide and corticosteroids such as ciclesonide (see col. 6, line 52 - col. 7, line 11 ) and (d) carrier particle size of approximately 10 to 500 μg (see col. 7, lines 40-53).

Nishimura et al. teaches an inhalation composition comprising anticholinergic agents, such as, oxitropium bromide and ipratropium bromide and corticosteroids such

as beclomethasone dipropionate for treating asthma (see the entire article, especially page 85, col. 2, Introduction; page 87, Table 1 and Discussion). Nishimura teaches the addition of oxitropium bromide to corticosteroids such as beclomethasone dipropionate shows beneficial effects (see page 87, col. 1, Discussion, 1st paragraph).

Banholzer et al. teaches esters of thienyl carboxylic acids and amino alcohols such as tiotropium and its salts as strong anticholinergic agents having prolonged action for use in treating asthma (see the entire article, especially col. 3, line 23 - col. 4, line 9; col. 5, compound A). Banholzer also teaches the compounds show similar toxicity to ipratropium bromide while at the same time the therapeutic effect is stronger (see col. 3, lines 27-32).

Based on the combination of the above cited references, the preparation of a dry powder inhalation formulation comprising an anticholinergic agent, such as a tiotropium salt and a corticosteroid, such as ciclesonide would have been obvious to the skilled artisan in the art at the time of the present invention. The motivation to combine an anticholinergic agent with a corticosteroid is based on (a) the knowledge in the art of the utilization of each in treating similar conditions such as asthma and (b) the teaching by Nishimura of the beneficial effect of a combination of an anticholinergic agent and a corticosteroid. The motivation to utilize tiotropium as the anticholinergic agent is based on the teaching of Banholzer of the stronger and prolonged therapeutic action of esters of thienyl carboxylic acids and amino alcohols.

The recitation of (a) weight ratios of anticholinergic to steroid (see claims 9 and 10); (b) capsule containing the claimed composition (see claims 25, 26, 31-37) and (c) a kit containing the claimed composition (see claims 63-66) are noted.

However, Banholzer teaches various formulations including capsules (see **'163**, col. 4, lines 3-9) and, thus, the recitation of capsules containing the claimed composition is prima facie obvious. Additionally, weight ratio of the active ingredients and kits are not patentable over the cited references as discussed above because (a) the court has held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 105 USPQ 233 and (b) incorporation of known agents into kits are well known in the medical art. Therefore, the instantly claimed invention would have been obvious to one of skilled in the art at the time of the present invention.

**(10) Response to Argument**

**1a**) Appellant argues the combination of references teachings fails to create a prima facie case of obviousness of the claimed invention and the Declaration under 37 CFR 1.132 provides clear and convincing evidence of the nonobviousness of the claimed invention. According to Appellant, (a) the synergism shown by the declaration of the specific combination versus the additive effect of the two components separately are surprising/unexpected, (b) Nishimura points only to an "additive effect" from the combination, (c) from Nishimura and the other references, the skilled artisan in the art could not have expected more than just an additive effect from a combination of anticholinergic and steroid and (d) Banholzer discloses a generic formula (I)

encompassing a range of compounds which includes tiotropium salts and the instant claims are directed particularly to tiotropium salts. Appellant's argument was considered but not persuasive for the following reasons.

As noted above in #9(I), (a) Nishimura teaches the combination of an anticholinergic agent and a corticosteroid shows beneficial effects and (b) Banholzer teaches theinyl carboxylic acids, such as tiotropium and its salts have therapeutic effects that are stronger and prolonged when compared to ipratropium bromide as disclosed by Nishimura. Therefore, the combination of an anticholinergic agent and a corticosteroid as presently claimed is made obvious by the cited references. Because tiotropium and its salts are taught by Banholzer to be stronger therapeutically than the anticholinergic agents of Nishimura, the skilled artisan would have the motivation to utilize said agents as the anticholinergic agent in a combination comprising corticosteroid for treatment of asthma as taught by Nishimura with the reasonable expectation of improvement in the treatment of asthmatic patients.

Appellant argues Nishimura points to an additive effect whereas the instant combination was shown to have a synergistic effect. However, for a showing of unexpected and unobviousness of the claimed invention, the examiner's position is that Appellant should make comparison between the closest prior art composition and the instantly claimed combination under similar conditions.

However, it is Appellant's position that the showing in the declaration of synergism is sufficient to overcome the obviousness rejection in the absence of a comparison of the claimed combination with the closest prior art combination.

According to Appellant, Nishimura teaches the advantages are only minor and there is no proof that the advantages are more than merely the additive effect.

The examiner agrees with Appellant's discussion of Nishimura. However, the first issue is whether based on the teaching of Nishimura, the skilled artisan would have been motivated to combine other corticosteroids and anticholinergic agents in treating asthma. The examiner position is that said would have been prima facie obvious to the skilled artisan in the art at the time of the present invention and, the motivation would be based on the reasonable expectation of improvement in the treatment of asthma utilizing a combination as taught by Nishimura.

The second issue is whether the showing in the declaration is sufficient to overcome the obviousness of the combination as taught by Nishimura. The examiner's position is that the showing is deficient in that (a) Appellant has not made comparison with the closest prior art composition in a true side-by-side comparison and (b) Appellant is arguing the results obtain in asthmatic human patients versus that obtain in beagle dogs. However, the two are different in a number of ways including the following:

| | Nishimura et al. | Decl. Of Dr. Bouyssou |
|---|---|---|
| Test species | Human asthmatic patients | Beagle dogs given repeated injection of acetylcholine to increase bronchial resistance (10-14 kg) |
| Dose of corticosteroid | 400-2400 µg/day | 0.1 mg/kg or 0.3 mg/kg |
| Dose of anticholinergic agent | 200 µg/day | 0.06 µg/kg or 0.1 µg/kg |

Appellant argues the comparison is not with Nishimura but between monotherapy with ciclesonide or tiotropium versus a combination of the drugs as shown in the declaration. The examiner agrees that if one looks just at those results, a reasonable argument of synergism can be made for a combination of 0.06 µg/kg tiotropium bromide in combination with 0.1 mg/kg of ciclesonide in beagle dogs:

> Compared to the efficacy of each mono-therapy, the combination of submaximal doses of ciclesonide (0.1 mg/kg) and tiotropium bromide (0.06 µg/kg) resulted in an unexpected super-additive bronchoprotection of 49 ± 7 % at 3 hours and of 41 ± 14 % after 24 hours.
>
> The combined administration of tiotropium bromide and ciclesonide resulted in a clearly synergistic bronchoprotection in this model. In particular at the lower doses of tiotropium bromide (0.06 µg/kg) in combination with ciclesonide (0.1 mg/kg) this effect appears to be significantly higher than the summarized values of the respective mono-therapies. This is quite apparent at 3 and 24 hours after inhalation of the test compounds.

(see page 4, paragraphs 4-5 of the declaration).

However, the combination of an anticholinergic agent and a corticosteroid is taught by the art as evidenced by Nishimura and there is no evidence on record that said results would be unobvious and/or unexpected when compared with the combination taught by Nishimura under similar conditions. As shown above, the results of Nishimura were obtained in humans whereas those of Appellant were obtained utilizing beagle dogs.

Additionally, Appellant argues the showing is also commensurate in scope with the claimed invention based on the narrow claim scope (see page 7, 1st full paragraph). It is noted that the declaration states, **"in particular at lower doses of tiotropium**

**bromide (0.06 µg/kg) in combination with ciclesonide (0.1 mg/kg) this effect appears to be significantly higher than the summarized values of the respective mono-therapies**" and does not provide any data of combination of higher doses and/or combination of high and low doses of each of tiotropium bromide and ciclesonide. Thus, based on Appellant's discussion of the results, the assumption is that the synergism shown by the declaration is also dependent on concentration of the active ingredients. Therefore, the showing is not commensurate in scope because the claims are not limited to the specific concentrations in the declaration showing synergism.

Lastly, Appellant argues the references provide no teaching regarding a composition containing "a pharmaceutically acceptable excipients selected from the group consisting of glucose, arabinose, lactose, saccharose and maltose" nor is there any teaching regarding the utilizing of the particular excipients with the particular combination of tiotropium and ciclesonide. However, the excipients noted above are well known excipients used in the preparation of powder formulations (see Keller noted in 9 II) above) and, thus, the use of said excipients in the preparation of a powder formulation containing tiotropium and ciclenoside would have been prima facie obvious. The fact that neither Nishimura nor Banholzer disclose said excipients does not make their utilization in dry powder formulation unobvious.

In summary, (a) Nishimura provides the skilled artisan in the art with motivation to combine an anticholinergic agent with a corticosteroid in treating an asthmatic patients based on the treating of significant improvement, (b) ciclesonide and tiotropium are well known corticorsteroid and anticholinergic agent, respectively and (c) Banholzer

provides ample reason to utilize tiotropium and its salts based on the teaching of prolonged action and stronger therapeutic property when compared with ipratropium bromide as taught by Nishimura. Appellant's showing of unexpected and unobvious results is not persuasive because the comparison is not a true side-by-side comparison with the closest prior art composition. The skilled artisan in the art would have a reasonable expectation of improvement in the treatment of asthmatic patients with any combination of anticholinergic agent and corticosteroid based on the teaching of Nishimura and, thus, the claimed invention is prima facie obvious.

**1b**) Appellant argues the additional distinction of the claims discussed in 1a regarding the failure of the cited prior art to disclose or suggest a composition with "a pharmaceutically acceptable excipients selected from the group consisting of glucose, arabinose, lactose, saccharose and maltose" does not apply to claim 39. Appellant's argument was considered but not persuasive for the following reasons.

Claim 39 recites a pharmaceutical composition "**consisting essentially of**" tiotropium salt and ciclesonide in the form of an inhalable powder. The phrase "consisting essentially of" as recited by claim 39 limits the scope of the claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention (MPEP § 2111.03). There is no evidence on record showing that the additional components would change the characteristics of Appellant's invention. In the absence of such a showing, the claimed invention is prima facie obvious based on the argument present above in 1a.

**2a**) Appellant's argument against Nishimura and Banholzer are as discussed above in 1a).

Additionally, Appellant argues Keller discloses adding magnesium stearate to powder formulations containing a wide variety of active agents including tiotropium and ciclesonide, separately, to improve their moisture resistance but does not provide a suggestion to specifically combine tiotropium and ciclesonide or one of the specific excipients recited in the current claims. Further, it is Appellant's position that Keller does not provide a hint that such a combination would provide unexpected synergistically advantageous properties as shown by Appellants. Appellant argument was considered but not persuasive for the following reasons.

Keller does not have to specifically teach a combination of tiotropium and ciclesonide nor a combination of said actives in combination with the specific excipients recited by the instant invention, i.e., glucose, arabinose, lactose, saccharose and maltose in order to provide a prima facie case of obviousness for the utilization of said excipients in the production of powder formulation containing said actives. As disclosed by Keller, the recited excipients are "**customarily**" used in dry powder formulation (see col. 8, lines 1-16). Each of tiotropium bromide and ciclesonide is noted by Keller as being capable of being incorporated in a dry powder formulation and, thus, combination of the two active agents in a dry powder formulation would have been prima facie obvious to the skilled artisan in the art at the time of the present invention. The motivation to combine the two active agents in dry powder formulation is based on the teachings of Nishimura and Banholzer as discussed above in 9 II).

As noted above in 1a) (a) Nishimura provides the skilled artisan in the art with motivation to combine an anticholinergic agent with a corticosteroid in treating asthmatic patients based on the teaching of significant improvement, (b) ciclesonide and tiotropium are well known corticorsteroid and anticholinergic agent, respectively, as evidenced by Keller and (c) Banholzer provides ample reason to utilize tiotropium and its salts based on the teaching of prolonged action and stronger therapeutic property when compared with ipratropium bromide as taught by Nishimura. The preparation of a inhalable powder formulation comprising tiotropium and ciclesonide and a carrier materials/excipients such as glucose, lactose, etc. as recited by the instant claims would be prima facie obvious based on the knowledge in the pharmaceutical art as evidenced by Keller. Appellant's showing of unexpected and unobvious results is not persuasive because the comparison is not a true side-by-side comparison with the closest prior art composition. The skilled artisan in the art would have a reasonable expectation of improvement in the treatment of asthmatic patients with any combination of anticholinergic agent and corticosteroid based on the teaching of Nishimura and, thus, the claimed invention is prima facie obvious.

**2b**) Appellant argues the additional distinction of the claims discussed in 2a regarding the failure of the cited prior art to disclose or suggest a composition with "a pharmaceutically acceptable excipients selected from the group consisting of glucose, arabinose, lactose, saccharose and maltose" does not apply to claim 39. Appellant's argument was considered but not persuasive for the following reasons.

Claim 39 recites a pharmaceutical composition "**consisting essentially of**" tiotropium salt and ciclesonide in the form of an inhalable powder. The phrase "consisting essentially of" as recited by claim 39 limits the scope of the claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention (MPEP § 2111.03). There is no evidence on record showing that the additional components would change the characteristics of Appellant's invention. In the absence of such a showing, the claimed invention is prima facie obvious based on the argument present above in 1a.

**(11) Related Proceeding(s) Appendix**

None

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Barbara Badio/
Primary Examiner, Art Unit 1628

Conferees:

/Brandon J Fetterolf/
Supervisory Patent Examiner, Art Unit 1628

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1627